MEVALONATE PATHWAY: ROLE OF BISPHOSPHONATES AND STATINS

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[Metabolismo del mevalonato: ruolo dei Bifosfonati e delle Statine]

SUMMARY

Aminobisphosphonates and statins act in the same metabolic way. Bisphosphonates are considered the drugs of choice for the treatment of osteoporosis, like statins for the treatment of atherosclerosis. Aminobisphosphonates inhibit cholesterol biosynthesis and this might be relevant for their actions on atherosclerosis too.

Recently, HMG-CoA reductase inhibitors (statins), have been correlated to protective effects on bone metabolism. Because of their widespread use, prevention of bone loss and fractures would be a desirable side effect. However, the mechanisms by which statins may affect bone metabolism and aminobisphosphonates may affect atherosclerosis are poorly defined.

Further studies are necessary to assess the effects of those drugs in combination or alone on the prevention of osteoporosis, atherosclerosis and other age-related diseases.

Key words: Bisphosphonates, statins, atherosclerosis, osteoporosis

RIASSUNTO

Aminobisfosfonati e statine agiscono sulla stessa via metabolica, la via del mevalonato. I bisfosfonati sono conside - rati i farmaci di scelta nel trattamento dell’osteoporosi, come le statine nel trattamento dell’aterosclerosi. Gli aminobisfosfo - nati inhibited la biosintesi del colesterolo e questo è rilevante per la loro azione anche contro la aterosclerosi.

Recentemente, gli inibitori della HMG-CoA riduttasi (statine), sono state correlate ad effetti protettivi sul metabolismo osseo. A causa del loro largo uso, la prevenzione della perdita di massa ossea e delle fratture, potrebbe essere un desiderabile effetto collaterale. Tuttavia, il meccanismo con cui le statine influiscono sul metabolismo osseo e gli aminobisfosfonati sulla aterosclerosi è ancora poco definito.

Ulteriori studi sono necessari per chiarire gli effetti di questi farmaci in combinazione o da soli nella prevenzione di osteoporosi, aterosclerosi ed altre patologie correlate all’età.

Parole chiave: Bisfosfonati, statine, aterosclerosi, osteoporosi

Role of Bisphosphonates (BPs)

Currently among the principal therapeutic options for the treatment of osteoporosis, BPs play a fundamental role, being powerful inhibitors of bone resorption. They are synthetic compounds with a high affinity for calcium containing crystals. They selectively concentrate at the bone level, on the active surface, binding to the crystals of hydroxyapatite.

Subsequently, they are locally released, absorbed by the bone cells where they are able to remain on the spot for long periods to be slowly released again during the phases of bone remodelling.

Chemically they are analogous to endogenous pyrophosphate (P-O-P) with an atom of carbon in the oxygen place. They contain two side chains R1 and R2 and two atoms of phosphorus linked to a single atom of carbon forming a P-C-P structure which is completely resistant to the enzymatic hydrolysis. The shortest chain binds to the mineral content of the bone tissue and the longest chain is responsible of the effectiveness of the bisphosphonates. Changes in the two side chains of the atom of carbon have produced a great number of different bisphosphonates, included those currently used in the clinical practice.

BPs are divided into first generation BPs as Etidronate and Clodronate and second generation BPs, characterized by an aminic terminal group (aminobisphosphonates) as Pamidronate and Alendronate.
A third generation of bisphosphonates has recently been discovered (Zoledronate) characterized by an aromatic chain\(^7\).

Aminobisphosphonates inhibit the mevalonate pathway, that through the intervention of various enzymes as the acetocetil-CoA sintetase, the HMG-CoA sintetase (\(\beta\)-hydroxi-b-metilglutaril-CoA sintetase), the HMG-CoA reduttase, the farnesil-disphosphate sintetase (site of action of the aminobisphosphonates), leads not only to the production of cholesterol, but also to isoprenoid lipids and geranil-geranil disphosphates which anchors some regulator proteins to the cell membranes.

Through isoprenilation, that needs guanosine triphosphatase (GTPase), these proteins regulate a variety of cellular processes required for the osteoclasts functions, included the determination of cell morphology, cell adhesion, and formation of the “ruffled border” and apoptosis\(^{10}\).

Among these regulator proteins there are also the Ras, Rac, Rho, intracell “signal” proteins, that translate extracellular signals, activating the different receptors.

It has been shown that the activation of the receptor of the interleuchin-6 (IL-6), made up of two components IL-6R and gp130, depends on the process of isoprenilation and implicates the expression of proteins such as Rac, to induce the production and the activation of IL-6 and therefore IL-6 mediate inflammation. The cells of the immune system such as monocytes, in the inflammatory sites require isoprenoid products to activate the NADPH oxidase to induce IL-6 activation. When the mevalonate pathway, and precisely the FPP sintetase is inhibited by aminobisphosphonates, leads to depletion of the isoprenoid products and therefore inhibition of the IL-6 mediated inflammation\(^{10}\).

Recent studies show that IL-6 mediate inflammation is involved in the physiopathogenesis of atherosclerosis, peripheral vascular pathologies, coronary atherosclerosis and other age-related disorders included osteoporosis, Alzheimer Disease and type 2 diabetes.

Particularly, in subjects without cardiovascular risk factors, only elevated levels of IL-6, among all the inflammatory markers, have shown to have predictive value for cerebral ischemic events and coronaryopathies, and these ones lead to myocardic contractility depression\(^9\).

It has also been hypothesized that the bisphosphonates may have also an antiatherosclerotic action on the animal model\(^{15,20}\).

This action is attributed to their ability to inhibit the etherotic calcification (calcium deposition in the soft tissues), even if their effectiveness in patients with this disease has not been sufficiently confirmed so far\(^9\).

It seems that the bisphosphonates accumulate in the arteries walls\(^{12,21}\). In a recent study on patients with type 2 diabetes and osteopenia, treated for one year with cyclical administration of etidronate, has been observed, with ultrasounds, a statistically significant reduction of the medial-intimal thickness of the carotid. These patients have not been observed to have alterations of cholesterol and triglycerides levels. Therefore, the antiatherogenic action of the bisphosphonate cannot be attributed to a possible systematic lowering serum fat action only\(^{10}\).

Nevertheless, some lipophil bisphosphonates reduce cholesterol levels when administered orally in vivo\(^{10}\).

**Role of the statins**

Statins inhibit the 3-hydroxi-3-metilglutaril CoA reductase (HMG CoA) which catalyze the conversion of the HMG CoA in mevalonate in the synthesis of cholesterol. Therefore statins could have effects on the bone (Fig.1).

Recent in vivo studies have underlined that the use of statins is related to increased bone mineral density (Wang et al 2000; Schoofs et al., 2004), suggesting that statins could have protective action on the bone. (Bauer et to the., 2004).

![Fig. 1: Mevalonate pathway](image)
protein 2 (BMP-2), a powerful activator of osteoblastic differentiation.

The administration of statins in animal models (lovastatin and simvastatin) leads to the neoforation of bone tissue of the skull near the point of the subcutaneous injection of the drug.

In ovariectomized rats, systematic administration of statins showed anabolic action on the bone\(^{(18)}\).

Luckman et al.\(^{(16)}\) have shown that the mevastatin has a powerful anti-osteoclastic effect in vitro and in vivo, leading to apoptosis of osteoclasts and macrophages.

This effect is similar to that one of aminobisphosphonates and is probably due to the inhibition of isoprenilation of some G proteins of the osteoclasts, but also of Ras and Rho proteins\(^{(18)}\).

The Ras protooncogene plays a main role in the phenotypic, morphological and functional osteoclasts maturation.

Van Beek et al.\(^{(19)}\) observed a powerful antiosteoclastic effect of mevastatin in the whole embryonic bones culture, similar to that one of ibandronate.

Previously studies on animal models have shown that statins were able to reduce corticoid-induced osteoporosis\(^{(17)}\).

The effect of atorvastatin on osteoblasts production of the receptor activator of the nuclear factor-kB ligand (RANKL) and of osteoprotegerin (OPG), an essential cytokine for the osteoclast cell biology has been recently studied. While RANKL promotes the osteoclastic formation and activation, with consequent bone resorption, OPG acts as soluble receptor that stops the effects of RANKL.

It has also been shown that atorvastatin increases the production of OPG from human osteoblasts blocking the mevalonate pathway. In fact, treating human osteoblasts with substrates of the biosynthesis of the cholesterol below the site of action of the HMG-CoA reductase (mevalonate, geranilgeranil pyrophosphate) cancelled out inducing effect of the atorvastatin\(^{(19)}\).

Atorvastatin administered together with risedronate produces a higher increase of bone mineral density (BMD) in comparison to that one observed with risedronate alone, in post menopausal women affected by osteopenia or osteoporosis and hypercholesterolemia.

In addition, the association of the two drugs shows more marked effects on the lipidic profile, particularly on total cholesterol and LDL, compared to the single treatment with statins\(^{(16)}\).

However, the study conducted by L. Rejnmark et Al. on postmenopausal women affected by osteopenia, treated with simvastatin for one year, did not underlined positive effects on the BMD or on bone turnover\(^{(11)}\).

Despite this, hydrophilic statins, as the pravastatin or other similar agents do not induce the bone morphogenic protein (BMP-2), and do not influence the risk of vertebral fracture, while the risk of vertebral fracture is reduced up to 50% in individuals older than 55 years, after prolonged treatment (more than 365 days) with lipophilic statins (atorvastatin, simvastatin, fluvastatin, lovastatin).

Statins, therefore, with their high affinity for bones, could potentially be used in the treatment of patients affected by hypercholesterolemia with osteoporosis, especially in the prevention of fractures\(^{(16)}\).

**Considerations**

Aminobisphosphonates and statins interfere with the mevalonate pathway, that is related not only to the synthesis of the cholesterol but also with bone metabolism.

In a recent study on rats, has been seen that a single dose of zoledronic acid reduces the osteolysis induced by the particles of polyethylene with a higher molecular weight, used in the arthroplasty of the hip, exactly as much as it has been reduced using sinvastatin. Both drugs could play a preventive and therapeutic role as antiresorptive agents in the osteolysis induced after surgical insertion of articular prosthesis\(^{(20)}\).

Statins develop their effects on bones both stimulating the expression of the BMP-2, interfering with the RANKL / OPG system and also with a mechanism similar to that one of aminobisphosphonates, i.e. inhibiting the formation of intermediaries (farnesil difosfato, geranilgeranil pyrophosphate) necessary for the isoprenilation of proteins that promotes the osteoclastic activity.

Experimental studies have demonstrated a dual action of these agents: antiatherogenic and bone antiresorptive.

On the contrary, bisphosphonates act through the depletion of the isoprenoid products, reducing inflammatory processes in an early phase of atherosclerosis.

Finally, the association with statins contributes to strengthen the limiting action on the vascular atherogenic progression.
Further studies will be fundamental to better define the way both molecules act, and also to assess the possibility to use only one drug that can effectively act both on the osteoporosis and on the dyslipidemia, in order to reduce the morbidity and mortality of these diseases.

References

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